Less Is More in Lung Cancer Risk Prediction Models

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Screening of high-risk individuals by low-dose chest computed tomography (CT) reduces lung cancer mortality, as has been shown by 2 large randomized clinical trials.[1,2] Contrary to other cancer screening programs, such as breast and colorectal cancer screening, individuals eligible for screening are not selected only based on sex and age. Lung cancer is in most cases diagnosed in (former) smokers. To increase the efficacy of a screening program, and to minimize harms to individuals at low risk of the disease, it is most cost-effective to invite only those individuals who have the highest risk of developing lung cancer to undergo annual low-dose chest CT. Risk prediction models aim to assist in identifying these high-risk individuals, and most international lung cancer screening guidelines recommend using a model to optimize selection of the screening population.[3]

In addition to prediction models for the identification of the population at risk, in recent years, a variety of models have been published predicting lung nodule malignancy risk in screen-detected pulmonary nodules. These lung nodule malignancy risk prediction models aim to improve decision-making regarding nodule management and diagnosis. In every second lung cancer screening participant, at least 1 lung nodule is detected at the baseline screening round. A quarter of those who undergo screening present with 2 or more baseline nodules.[4] At nodule level, fewer than 1% are diagnosed as lung cancer; the others are likely to represent benign lesions such as scars or intrapulmonary lymph nodes.

Lung nodule malignancy prediction models are based either on data collected in screening studies (ie, different versions of the model used in the Pan-Canadian Early Detection of Lung Cancer Study [also referred to as the Brock model][5] and the model using data from the UK Lung Cancer Screening [UKLS] trial[6]) or on clinically, mostly incidentally, detected nodules (ie, models from the Mayo Clinic, the US Department of Veteran Affairs clinics, and Peking University People's Hospital).

In the study by González Maldonado et al,[7] performance of these lung nodule malignancy prediction models was externally tested using data from the interventional group of the German Lung Cancer Screening Intervention (LUSI) randomized clinical trial. In total, 1159 participants with 3903 noncalcified lung nodules in any of 5 annual low-dose CT screening rounds were selected for this study. During the active screening period, 54 of 1159 participants with nodules (5%) were diagnosed with lung cancer. Most lung nodules were detected at baseline (2883 nodules [73.9%]), whereas half of the lung cancers were diagnosed in 1 of the 1020 nodules newly detected after baseline. In the rounds following baseline screening, 80.6% of lung cancers had diameter of at least 8 mm at diagnosis.

González Maldonado et al[7] have shown that performance of all 8 prediction models was better on prevalence (baseline) nodules compared with nodules newly detected during incidence screenings. Previous studies have shown that lung nodule malignancy risk differs between nodules present at baseline and new nodules. In general, new nodules identified at incidence screening are relatively young and fast growing whereas baseline nodules might have been present for years. This leads to a substantially lower overall lung cancer probability at baseline.[8] Therefore, new nodules are managed differently from baseline nodules in established guidelines.[3] This study shows that a different model for prediction of risk for malignant nodules should be developed for lung nodules newly detected after the baseline screening round.

Focusing on the models that were generated based on screening data, the different versions of the Pan-Canadian model outperformed the UKLS model. Sometimes less is more. In case a model includes parameters with high risk of interreader variability, such as diagnosis of bronchitis or

discrimination between part-solid and nonsolid lung nodules in the UKLS model,[6] transferability to other cohorts could be improper. González Maldonado et al[7] showed significantly better performance of the UKLS model in the LUSI data set after excluding parameters prone to volatility from the model.

Before drawing conclusions about the optimal lung nodule malignancy risk prediction model for lung nodule management in low-dose CT lung cancer screening based on this feasibility study, it is important to realize the study's limitations. In the LUSI trial, nodule size was determined based on 3-dimensional nodule segmentation instead of manual caliper measurements in the axial plane, leading to more precise and reproducible diameter measurements. Performance of the models in a manual nodule diameter-based lung cancer screening trial is expected to be worse. Furthermore, using semi–3-dimensional nodule measurements (diameter based on the nodule in 3 dimensions) might have masked a difference in performance of the diameter and volume versions of the Pan-Canadian model.

What are the main messages from the feasibility study of González Maldonado and colleagues[7] on different lung nodule malignancy risk prediction models in an external low-dose chest CT lung cancer screening data set? First, this study showed the importance of external testing of risk prediction models. It found that the original results of some risk prediction models cannot be repeated in an external set. One reason, as illustrated by González Maldonado et al,[7] might be inclusion of parameters prone to high volatility in a risk prediction model, reducing the transferability to an external data set. Second, the sharply reduced model performance when using the different models on nodules newly detected after baseline confirms the need of separate management for new nodules. This is also true with respect to nodule malignancy risk prediction models.

ARTICLE INFORMATION

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REFERENCES

1. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409. doi:10.1056/NEJMoa1102873

2. De Koning H, Van Der Aalst C, Ten Haaf K, Oudkerk M. Effects of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population based trial. *J Thorac Oncol*. 2018;13(10)(suppl):S185. doi:10.1016/j.jtho.2018.08.012

3. Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on lung cancer screening. *Lancet Oncol*. 2017;18(12):e754-e766. doi:10.1016/S1470-2045(17)30861-6

4. Heuvelmans MA, Walter JE, Peters RB, et al. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: the NELSON study. *Lung Cancer*. 2017;113:45-50. doi:10.1016/j.lungcan.2017.08.023

5. Tammemagi M, Ritchie AJ, Atkar-Khattra S, et al; Pan-Canadian Early Detection of Lung Cancer Study Group. Predicting malignancy risk of screen-detected lung nodules-mean diameter or volume. *J Thorac Oncol*. 2019;14(2):203-211. doi:10.1016/j.jtho.2018.10.006

6. Marcus MW, Duffy SW, Devaraj A, et al. Probability of cancer in lung nodules using sequential volumetric screening up to 12 months: the UKLS trial. *Thorax*. 2019;74(8):761-767. doi:10.1136/thoraxjnl-2018-212263

7. González Maldonado S, Delorme S, Hüsing A, et al. Evaluation of prediction models for identifying malignancy in pulmonary nodules detected via low-dose computed tomography. *JAMA Netw Open*. 2020;3(2)e1921221. doi: 10.1001/jamanetworkopen.2019.21221

8. Walter JE, Heuvelmans MA, de Jong PA, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. *Lancet Oncol*. 2016;17(7):907-916. doi:10.1016/S1470-2045(16)30069-9